PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

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ALLEMAGNE

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	12.08.2004
Applicant's or agent's file reference	**IMPORTANT NOTIFICATION**
28116P WO	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 03/06591	23.06.2003	01.07.2002

Applicant
WILEX AG et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 28116P WO	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/06591	International filing date *(day/month/year)* 23.06.2003	Priority date *(day/month/year)* 01.07.2002
International Patent Classification (IPC) or both national classification and IPC A61K39/395		
Applicant WILEX AG et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
01.10.2003	12.08.2004
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Le Flao, K Telephone No. +31 70 340-1040

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/06591

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-19 as originally filed

Claims, Numbers

1-17 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-17 (industrial applicability)

   because:

   ☒ the said international application, or the said claims Nos. 1-17 (method of treatment) relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-17
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-17
Industrial applicability (IA)	Yes:	Claims	
	No:	Claims	1-17

2. Citations and explanations

   see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1-17 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: BECK JOACHIM ET AL: "A Phase I/II trial with monoclonal antibody WX-G250 in combination with low dose interleukin-2 in metastatic renal cell carcinoma" PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL, vol. 43, March 2002 (2002-03), page 910 XP008023397 93rd Annual Meeting of the American Association for Cancer Research; San Francisco, California, USA; April 06-10, 2002, March, 2002 ISSN: 0197-016X

D2: LIU ZHANQI ET AL: "Anti-renal cell carcinoma chimeric antibody G250: Cytokine enhancement of in vitro antibody-dependent cellular cytotoxicity" CANCER IMMUNOLOGY IMMUNOTHERAPY, vol. 51, no. 3, May 2002 (2002-05), pages 171-177, XP001172419 ISSN: 0340-7004

D3: BLEUMER I ET AL: "A phase II trial with monoclonal antibody WX-G250 in advanced renal cell carcinoma" EUROPEAN UROLOGY SUPPLEMENTS, vol. 1, no. 1, January 2002 (2002-01), page 112 XP001164270 XVIIth Congress of the European Association of Urology; Birmingham, England, UK; February 23-26, 2002 ISSN: 1569-9056

NOVELTY and INVENTIVE STEP

D1 (XP008023397) discloses the co-administration of WX-G250 and of IL-2 at a low dose for treating metastatic renal cell carcinoma (abstract). The subject-matter of claims 1-7,10-17 is therefore not new (Article 33(2) PCT).

Claim 2 is considered to involve neither novelty nor inventive step for the following reasons. D1 discloses the use of the antibody cG250 in combination with IL-2 for the treatment of metastatic renal cell carcinoma (RCC). IL-2 is administered daily at low dose subcutaneously in an alternative pulsing scheme, cG250 weekly at the dose of 20 mg intravenously. The treatment is given for 3 months (see the abstract).

Although it is not stated that IL-2 is given prior to cG250, it can be implicitly derived from D1 that either IL-2 or cG250 is given at first. As a matter of fact the products are not administered together since cG250 is administered by iv infusion and IL-2 subcutaneously. The order of administration would be an essential feature (ie. conferring novelty over D1) if the effect ie. the treatment of patients with metastatic RCC would work only if one of the both products, IL-2, is administered at first. It appears from D1 that the combined therapy is effective and presents anti-tumour activity. Therefore it can be concluded that either (i) the order is essential but is disclosed in D1 since the effect is achieved or (ii) the order is not essential whereas the combination of IL-2 and cG250 is, regardless of the order of administration. Moreover changing a protocol or improving a protocol of a known effective treatment cannot be considered as involving an inventive step since the effect to be achieved (ie the treatment of patients with metastatic RCC) is expected. Therefore neither novelty nor inventive step is acknowledged to the subject-matter of claim 2.

D2 (XP001172419) discloses that IL-2 and IFN-alpha enhance and maintain the cG250-mediated ADCC of target RCC cells expressing G250 antigen (p.175, right-hand column, l.1 to p.176, left-hand column, l.31). The therapeutical interest of such co-administration is proposed for treating renal cell carcinoma (p.177, left-hand column, first paragraph). The subject-matter of claims 1-17 is therefore not new (Article 33(2) PCT).

INDUSTRIAL APPLICABILITY

For the assessment of the present claims 1-17 on the question whether they are

industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

CLARITY and SUPPORT

Claims 1 and 2 are not supported by the description as required by Article 6 PCT, as their scope is broader than justified by the description. The reasons therefor are the following: serious doubts are objected to the fact that such co-administration has an effect with any cytokine and any anti-tumour antibody for any tumour. Since in the description it is only referred to WX-G250, to IL-2, to IFN-alpha and to renal cell carcinoma, the scope of the claims should be restricted.

The terms continuously, repeatedly and low-dose form used in claim 1 and the terms substantially constant dose used in claim 10 are vague and unclear and leave the reader in doubt as to the meaning of the technical features to which they refer, thereby rendering the definition of the subject-matter of said claim unclear (Article 6 PCT).

Claim 3 does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not defined. The claim attempts to define the subject-matter in terms of the result to be achieved. In this instance such a formulation is not allowable because it appears possible to define the subject-matter in more concrete terms, viz. in terms of how the effect is to be achieved.